

Practitioner's Docket No. MPI95-015P1RCPA1DV1M**USSN 09/801,089****REMARKS**

Claims 1-20 and 24-29 have been canceled. Claims 35-40 have been withdrawn pending allowance of a generic claim. Claims 21-23 and 31 have been amended. Claims 21-23 and 30-34 are under present consideration.

Claim 21 has been amended to add a step which connects integrin phosphorylation to signaling. Support for the amendment can be found in the Specification at, for example, page 37, lines 15-17. Claim 21 also has been amended to recite "outside-in or inside-out signaling." Support for the amendment can be found in the Specification at, for example, page 45, line 25.

Claim 22 has been amended to delete the step of separating the components of the extract. Support for this amendment can be found in the Specification at, for example, page 37, lines 19-21.

Claim 23 has been amended to update antecedence after amending claim 22.

Claim 31 has been amended to clarify the method. Support for this amendment can be found in claim 22 as filed.

The amended claims find support in the application as originally filed. The Amendment does not add new matter. Further remarks are set forth below with reference to the numbered paragraphs of the Office Action.

Paragraph 4. Rejection of Claims 21-23 and 30-34 Under 35 U.S.C. §112, Second Paragraph

Claims 21-23 and 30-34 were rejected under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps. The Examiner concluded that the omitted step comprises some sort of determination regarding how the phosphorylation state of an integrin is connected to signaling. In response, Applicants have amended claim 21 (claims 22, 23 and 30-34 dependent thereon) to recite that phosphorylation in the integrin cytoplasmic domain indicates integrin-mediated signaling. In view of this amendment, Applicants request that this rejection be withdrawn.

Paragraph 5. Rejection of Claims 21-23 and 30-34 Under 35 U.S.C. §112, Second Paragraph

Claims 21-23 and 30-34 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that the term "signaling" in claim 21 is vague and indefinite as it is undefined. The Examiner notes that the Specification describes outside-in and inside-out signal transduction, but any other types would be difficult to determine as part of the invention. In response, Applicants have amended claim 21 (claims 22, 23 and 30-34 dependent thereon) to recite

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"outside-in and inside-out" when referring to the integrin-mediated signaling. In view of this amendment, Applicant requests that this rejection be withdrawn.

Paragraph 7. Rejection of Claims 22-23 and 30-34 Under 35 U.S.C. §112, First Paragraph

Claims 22-23 and 30-34 were rejected under 35 U.S.C. §112, first paragraph for lack of written description of the claimed invention, that the disclosure does not reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner contends that the steps of claim 22 and the limitations of claims 23 and 30-34 do not have support from the specification or the claims as originally filed.

In response, Applicants have amended claim 22 to more closely align the steps with statements from the specification. As for the limitations of claims 23 and 30-34, Applicants follow with more precise information identifying some support for these claims. Support for claim 23 can be found in the specification, at, for example, page 41, line 18; page 54 line 20; and page 57, lines 4-5. Support for claim 30 can be found at, for example, page 43, line 14. Support for claim 31 can be found in claim 22 as filed. Support for claim 32 can be found at, for example, page 38, line 2; page 43, line 15; page 54, line 19; and page 57, line 4. Support for claim 33 can be found at, for example, page 37 line 26. Support for claim 34 can be found at, for example, page 54, line 16 and page 57, line 3. In view of these amendments and remarks, Applicants respectfully ask that this rejection be withdrawn.

Paragraph 9. Rejection of Claims 21-23 and 30-34 Under 35 U.S.C. §103(a)

Claims 21-23 and 30-34 were rejected under 35. U. S.C. §103(a) as being unpatentable over Huang et al. in view of Agrez et al.. The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art to use the antiphosphotyrosine antibody as taught by Huang et al. while employing the carcinoma cell in which Agrez et al. identified the importance of an integrin β subunit for proliferation to identify integrin mediated signaling by phosphorylation of a β subunit cytoplasmic domain. Applicants respectfully traverse this rejection.

The combination of these references does not teach all the elements of the claimed invention. Huang et al. uses the antiphosphotyrosine antibody to look for tyrosine phosphorylation of pp125^{PAK}, a 125 kDa protein tyrosine kinase previously shown to be phosphorylated on tyrosine residues in response to platelet aggregation. In contrast, as the present Specification discloses, no phosphorylation had been observed for any integrin performing integrin mediated signaling. Therefore, one must look to Agrez et al. to find the teaching that phosphorylation of a beta integrin is important for integrin mediated signaling in carcinoma cells. However, a review of Agrez et al. does not result in such a finding. Instead, one finds a comparison of the cytoplasmic domains of $\beta 1$, $\beta 3$ and $\beta 6$ integrins (Figure 3a) accompanied by a general statement about regions required for focal contact localization. In addition, one finds the major

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result of the Agrez et al. study, that the 11 C-terminal residues of $\beta 6$ integrin are important for the proliferation of $\beta 6$ integrin-containing cells. One does not find a discussion of tyrosine phosphorylation in this integrin or the others. In fact, a review of the 11 C-terminal residues does not reveal any tyrosines. Therefore, it would be impossible for these important 11 C-terminal residues to use tyrosine phosphorylation as their mechanism to mediate proliferation of the carcinoma cells. Likewise, it would be impossible to use Huang et al.'s antiphosphotyrosine antibody on these 11 C-terminal residues to find integrin mediated signaling. Therefore, the Agrez et al. publication does not teach that phosphorylation of the cytoplasmic domains of β subunits of integrins are important for integrin mediated signaling. Without such teaching, a combination of the references does not give one of ordinary skill in the art a reasonable expectation of success that combining these references would result in the claimed invention. Withdrawal of the rejection is respectfully requested.

CONCLUSION

The foregoing amendments and remarks are being made to place the Application in condition for allowance. Applicants respectfully request the timely allowance of the pending claims because, in view of these amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. § 112 and 35 U.S.C. § 103(a) are overcome. Applicants believe that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned. If the Examiner disapproves of Applicants' amendments and remarks in this response, Applicants request a prompt mailing of a notice to that effect.

This paper is being filed timely within the three month period for response. No extensions of time are required. In the event any extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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